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(54) **Controlled release compositions for treating memory impairment**

(57) Arecoline, physostigmine, naloxone, nicotine or derivatives thereof are used in controlled release forms, e.g. as transdermal devices or as oral osmotic release devices, to treat memory impairment.

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SPECIFICATION

Devices and methods for treating memory impairment

The present invention is directed to devices and methods for treating memory impairment. More particularly, the present invention is directed to providing devices for the controlled release of compounds effective in treating memory impairment, and to methods for treating memory impairment comprising such controlled release. Senile dementia of the Alzheimer's type (SDAT), a pervasive and devastating affliction mainly affecting the elderly, is an example of memory impairment, the treatment of which is the goal of the present invention.

Acetylcholine is believed to be involved in learning and memory mechanisms; see Sitaram et al, Science, 201, 274 (1978), and Davis et al, Science, 201, 272 (1978). The Sitaram et al and Davis et al articles suggest that arecoline, a cholinergic agonist, and physostigmine, an acetylcholinesterase inhibitor, respectively, may be effective in treating memory impairment. Christie et al, however, have suggested that neither arecoline nor physostigmine offers a practical therapy for SDAT; see the British Journal of Psychiatry, 138, 46 at 49 (1981). This may, at least in part, be due to the short-lived effects of these compounds as suggested in the "Progress Report on Senile Dementia of the Alzheimer's Type" dated February 19, 1981 prepared by Marian Emr of the National Institute on Aging at page 20.

Naloxone is also believed to be effective in treating memory loss; see Chemical and Engineering News, 32 (March 28, 1983). The use of naloxone for treating SDAT is, however, still under investigation; see FDC Reports of March 21, 1983.

There is, therefore, a need for developing devices and methods for treating memory impairment, especially SDAT, practically and effectively. Accordingly, the objects of the present invention are: devices and methods effective in treating memory impairment, devices and methods which provide for the controlled release of compounds effective in treating memory impairment; processes for the manufacture of said devices and devices and methods for treating memory impairment by means of the controlled release of arecoline and derivatives, physostigmine and derivatives, naloxone and derivatives, and nicotine and derivatives.

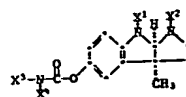
The above and other objectives as will become apparent from the following description have been achieved by providing a device for treating memory impairment comprising an effective amount of a compound selected from formula I,



(I)

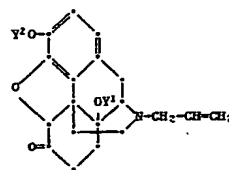
wherein R¹ represents hydroxy, lower alkoxy, or

NR³R⁴ and R², R³ and R⁴ independently represent hydrogen or lower alkyl; formula II,



(II)

60 wherein X¹, X², X³ and X⁴, independently represent hydrogen or lower alkyl; formula III,



(III)

wherein Y¹ and Y² independently represent hydrogen, lower alkyl or lower alkylcarbonyl (lower alkanoyl); and formula IV,



(IV)

65 wherein Z represents hydrogen or lower alkyl; and a means for delivering the compound at a continuous, controlled rate and to methods for treating memory impairment using such devices.

The effective compounds of the present invention include arecoline, physostigmine, naloxone, and nicotine. Some derivatives are also included in the invention.

Arecoline and arecoline derivatives have formula as shown and defined ahead. Arecoline is the compound of formula I, wherein R¹ represents methoxy and R² represents methyl.

Physostigmine and physostigmine derivatives may be represented by formula II as shown and defined ahead. Physostigmine is the compound of formula II, wherein X¹, X² and X³ represent methyl and X⁴ represents hydrogen.

Naloxone and naloxone derivatives may be represented by formula III as shown and defined ahead.

Naloxone is the compound of formula III, wherein Y¹ and Y² represent hydrogen.

Nicotine and derivatives may be represented by formula IV as shown and defined ahead.

Nicotine is the compound of formula IV, wherein Z is methyl.

In the compounds of the present invention, the term "lower alkyl" and "lower alkoxy" refer to alkyl and alkoxy groups having up to and including 7 carbon atoms and preferably up to and including 4 carbon atoms. Some examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, secondary butyl, tertiary butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, and heptyl. Some examples of alkoxy groups include methoxy, ethoxy, propoxy and butoxy.

Accordingly, the preferred compounds having formula I are those wherein R¹ represents hydroxy or lower alkoxy having up to 4 carbon atoms, such as methoxy, ethoxy, and isopropoxy, and R² represents hydrogen or lower alkyl having up to 4 carbon atoms

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such as methyl, ethyl, and isopropyl. The preferred compounds having formula II are those wherein X^1 , X^2 , X^3 , and X^4 represent hydrogen or lower alkyl having up to 4 carbon atoms such as methyl, ethyl and isopropyl. The preferred compounds having formula III are those wherein Y^1 and Y^2 represent hydrogen or lower alkyl having up to 4 carbon atoms such as methyl, ethyl, and isopropyl. The preferred compounds having formula IV are those wherein Z represents hydrogen or lower alkyl having up to 4 carbon atoms such as methyl, ethyl, propyl or isopropyl.

The most preferred compound having formula I is arecoline wherein R^1 represents methoxy and R^2 represents methyl. The most preferred compound having formula II is physostigmine wherein X^1 , X^2 and X^3 represent methyl and X^4 represents hydrogen. The most preferred compound having formula III is naloxone wherein Y^1 and Y^2 represent hydrogen. The most preferred compound having formula IV is nicotine wherein Z represents methyl.

The present invention further includes pharmaceutically acceptable carboxylate salts of compounds containing a carboxyl group and pharmaceutically acceptable acid addition salts of compounds containing amino groups. Some suitable carboxylate salts include, for example, alkali metal salts, e.g. the sodium or potassium salts; and ammonium salts. Some suitable acid addition salts of compounds containing an amino group include salts of mineral acids, e.g. hydrohalic acids, such as the hydrochloride or hydrobromide salt, and salts of carboxylic acids, e.g. salicylate, and tartrate salts.

An especially preferred embodiment of the present invention is a device containing, and a method utilizing, a mixture of compounds having formula I in combination with a compound having formula II. Preferably, the compound having formula I is arecoline and the compound having formula II is physostigmine. The weight ratio of the compound having formula I to the compound having formula II is 2-40:1, preferably 4-30:1, and most preferably 6-20:1.

The compounds of the present invention may be obtained commercially or may be synthesized by methods known in the prior art. Commercially, arecoline may be obtained from Inland Alkaloid Company, St. Louis, Missouri. Physostigmine may be obtained from O'Neil, Jones and Feldman Pharmaceuticals. Naloxone may be obtained from Endo Laboratories, Inc.

The compounds of formula I including arecoline may also be obtained by the partial hydrogenation of nicotinic acid. The hydroxy group may optionally be converted into lower alkoxy or amino optionally substituted by lower alkyl.

The compounds having formula II other than physostigmine may be prepared from physostigmine or by the same general methods used to prepare physostigmine.

The compounds having formula III other than naloxone wherein Y^1 and Y^2 represent hydrogen may be prepared from naloxone by converting the hydroxy groups into the corresponding lower alkoxy groups.

The compounds having formula IV other than

nicotine wherein Z represents methyl may be prepared from nicotine or by the same general methods used to prepare nicotine.

The present invention is directed more specifically to a device containing a means whereby a compound as described above is administered at a continuous, controlled rate. Such devices are already known in the prior art. The administration of pharmaceutically active compounds from such devices may be transdermal or oral.

Some suitable transdermal devices are described in US Patents 3,742,951, 3,797,494, 3,996,934, and 4,031,894. These devices generally contain a backing member which defines one of its face surfaces, an active agent permeable adhesive layer defining the other face surface and at least one reservoir containing the active agent interposed between the face surfaces. Alternatively, the active agent may be contained in a plurality of microcapsules distributed throughout the permeable adhesive layer. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

In another device for transdermally administering the compounds in accordance with the present invention, the pharmaceutically active compound is contained in a matrix from which it is delivered in the desired gradual, constant and controlled rate. The matrix is permeable to the release of the compound through diffusion or microporous flow. The release is rate controlling. Such a system, which requires no membrane is described in US patent 3,921,636. At least two types of release are possible in these systems. Release by diffusion occurs when the matrix is non-porous. The pharmaceutically effective compound dissolves in and diffuses through the matrix itself. Release by microporous flow occurs when the pharmaceutically effective compound is transported through a liquid phase in the pores of the matrix.

The device suitable in the present invention may also deliver pharmaceutically effective compounds orally. In one such device, the pharmaceutically effective compound is encapsulated in a semi wat r-insoluble membrane such as cellulose acetate. A tiny orifice is provided in the encapsulating agent by means of a drill or a laser. When placed in the body of the patient or animal being treated, water is absorbed through the encapsulating material. The pharmaceutically effective compound is forced through the orifice by osmotic pressure in the desired, gradual, constant, and controlled manner. Such systems are described in US patents 3,760,805, 3,760,806, 3,764,984, 3,845,770, 3,916,899, and 3,987,790. In these systems, the pharmaceutically active compound may be in solid form or absorbed on ion exchange resins as in the so called Penkinetic system.

Another system for oral administration in accordance with the present invention is described by Sheth

and Leeson in US patent 4,137,300. This patent describes a device containing a wax matrix.

The active compounds of the present invention are administered from a suitable device in any convenient and appropriate form. Liquid active agents may be administered in their pure form or in solution. Solid active compounds may be administered in solution or in suspension. The solvent or suspension medium may be aqueous or organic in nature.

Suitable solvents or suspension media for compounds having formula I are water, ethanol, silicone fluid, and mineral oil.

In order to facilitate the administration of a compound from a device as described above, a flux enhancer may be added to the system. In a device for transdermal administration, the flux enhancer increases the rate across the skin. An example of a flux enhancer for a transdermal device is "azone"; see US patent 3,989,816. Azone has the following formula:



Azone may be placed on the skin in contact with the device, or may be contained in a reservoir optionally in the presence of a co-solvent. Other flux enhancers for transdermal devices include alcohols such as ethanol, dimethylsulfoxide, decyl methyl sulfoxide, and N-methyl lauramide.

Oral devices contain flux enhancers in order to increase the rate of release of the pharmaceutically effective compound from the device. Some suitable flux enhancers for oral devices include, for example, polyethylene glycol, hydroxypropyl methyl cellulose, and sugar.

Other materials may be added to the device along with the active compound. In a transdermal system, the rate of absorption through the skin may be dependent on pH. If so, a buffer may be introduced into the device in order to provide the optimum pH.

It is also desirable to introduce an anticholinergic agent which does not cross the blood brain barrier along with the active compound in order to block peripheral cholinergic side effects. Some suitable examples of anticholinergic agents include methscopolamine bromide; Sitaram et al, *Science*, 201, 274 (1978), and homatropine methyl bromide.

The present invention is further directed toward a method for treating memory impairment such as SDAT. The method comprises the oral or transdermal administration at a gradual, constant, and controlled rate of a compound in accordance with the present invention to a warm-blooded animal, such as a human being or other mammal. The dose is that effective to treat memory impairment, i.e., SDAT. For example, arecoline and its derivatives are administered at a rate of 0.1 to 10 mg/hr, preferably 0.5 to 5 mg/hr. Physostigmine and its derivatives are administered at a rate of 0.05 to 3 mg/hr, preferably 0.1 to 1 mg/hr. Naloxone and its derivatives are administered at a rate of 0.01 to 5 mg/hr, preferably 0.02 to 2 mg/hr. Nicotine and its derivatives are administered at a rate of 0.02 to 2.5 mg/hr, preferably 0.05 to 2 mg/hr.

The preferred devices and methods of the present invention are devices and methods for the transdermal administration of arecoline.

The partition coefficient (K) of a compound between an aqueous phase and mineral oil has been used as an indication of its potential to diffuse across skin. Permeability appears to be optimal when the partition coefficient is 1. Arecoline in pH 10 buffer (99.9% dissociation to the free base) yields partition coefficients of 0.756 and 0.654 for concentrations of 1.0 M and 0.01 M, respectively. Thus, arecoline in its free base form is expected to have good in vitro transdermal flux.

In order further to test the permeability of arecoline to human skin, the transdermal diffusion of aqueous arecoline was monitored using human cadaver skin mounted in a Franz diffusion cell; see *Current Problems in Dermatology*, 7, 58 (1978) and the description of Franz diffusion cells and apparatus published by the Crown Glass Company. The flux, J, of each solution was calculated from a plot of change in concentration versus time.

The transdermal diffusion of arecoline was studied in several aqueous buffers from pH values of 6.4 to 9.0. This data is shown in Table 1. It is apparent that the rate of arecoline diffusion increases with increasing pH values.

Most of the skin samples were obtained from the back area of human cadavers. There was no systematic study to determine if the choice of donor-side would change the rate; however, it is presumed that the rate will be fastest in portions of the anatomy where the stratum corneum is relatively thin (chest, back, anterior forearm) and slowest where the stratum corneum is thickest (heel of hand, bottom of foot). There does not appear to be any difference in rate between Caucasian and Negro skin at pH values of 8 and 9. However, differences were observed between these two skin types in experiments at lower pH values.

The free base of arecoline appears to be the species that transfers across the stratum corneum. This allows some control of the transdermal flux by adjusting the pH value of the arecoline-containing solution. At a pH value of 9.0, approximately 85 mg can be transferred across 5 cm² in 24 hours. This amount is in the upper range of useful doses for administration of arecoline. Lower doses can be administered by reducing the surface area and/or pH value. The formulator will therefore have a great deal of flexibility in designing a system that has the desired delivery characteristics.

A problem encountered with arecoline is its instability in solution. In alkaline buffers, the free base rapidly hydrolyzes. Oxidation may also be a route of degradation.

This difficulty may be controlled by limiting the pH value of the solution or by using an appropriate non-hydroxylic vehicle.

The rate and extent of arecoline delivery across human skin can be controlled by several factors. If zero order transfer is desired, it can be achieved by maintaining an excess of arecoline in the delivery vehicle. As long as this concentration remains constant, the rate will be a zero order function which

can be limited in a transdermal device, for example, by a suitable membrane. The rate can be increased by increasing the surface area of the delivery system, increasing the concentration in the vehicle, or increasing the free base concentration by elevating the pH value.

Having generally described the invention, a more complete understanding can be obtained by reference to certain specific examples, which are provided herein for purposes of illustration only and are not intended to limit the claims unless otherwise specified.

TABLE I

TRANSDERMAL DIFFUSION OF ARECOLINE

pH of 1M Solution	Type of Skin *	Race of Skin Donor †	Flux (cg/cm ² /hr.)	Mean Flux
6.4	RC	N	0.017	0.017
7.0	RB	C	0.0545	0.069*
			0.0678	
			0.0833	
			0.0101	
7.5	RB	C	0.0057	0.105*
			0.1651	
			0.1486	
			0.2246	
8.0	LB	C	0.2003	0.448
			0.0383	
			0.4524	
			0.3817	
9.0	LB	C	0.5000	0.837
			0.4568	
			0.8551	
			0.8868	
	LB	N	0.8154	
			0.7419	
			0.8879	

* RC = Right Chest † N = Negro
 RB = Right Back C = Caucasian
 LB = Left Back

* Mean Flux does not include the Negro skin at these pH's as in these experiments diffusion through Negro skin was found to be significantly lower than that of Caucasian skin.

EXAMPLES

1. Preparation of Arecoline Free Base

Ten grams of arecoline hydrobromide are dissolved in a minimal quantity (approximately 25 ml) of water and adjusted to pH 10 with saturated potassium hydroxide solution in a separatory funnel. One hundred millilitres of petroleum ether are added and the layers are mixed. Sodium chloride is then added to saturate the aqueous layer. The organic layer is collected, and the aqueous layer is extracted three more times with petroleum ether. The combined organic layers are transferred to a 500 ml round bottom flask, boiling chips are added and the petroleum ether is removed by distillation. The remaining oil is layered with nitrogen and stored in low-actinic glassware. The oil is analyzed by NMR to show the absence of a halogen component.

2. Transdermal Diffusion of Arecoline Through Human Skin

Franz diffusion cells utilize the finite dose technique of *in vitro* drug delivery. Human cadaver skin is mounted in a diffusion chamber where it remains in constant contact with solution on both sides. The stratum corneum is in contact with a thin layer of concentrated drug in solution (donor side). The

receiver side contains a constantly stirred, isotonic saline solution maintained at 32°C. Diffusion of the compound is monitored by removing aliquots from the receiver side and analyzing these samples by HPLC.

The human skin used in all experiments is obtained from a medical school. All cadavers are refrigerated at death and excision is performed within 24 hours post-mortem. The skin is first treated with Betadine surgical scrub (Povidon-Iodine solution) and surfactant (the skin is scrubbed if dirty), rinsed with sterile water and then with Betadine rinse solution. The skin is then air-dried and swabbed with mineral oil prior to excision. A dermatome is used for excising the skin to -0.0015 in. (-350 microns) thickness. Saline solution is used to rinse the excess mineral oil from the skin prior to treatment with Eagle's minimole essential medium (minerals, amino acids and sugars). To this solution 15% glycerol is added and the skin is allowed to set for two hours. It is then removed from solution, packaged and frozen in liquid nitrogen. The samples, packed in dry ice are shipped in styrofoam containers and kept frozen until use.

For the flux experiments, skin samples are removed from the freezer and thawed immediately prior to use. The samples are examined visually for any tears or holes, then cut into smaller pieces, peeled from the gauze backing and mounted across the diffusion chamber with the stratum corneum side up. The donor-side cap is placed on top and the unit is clamped in place. The receiver-side is filled with a saline solution and stirred. The material in the receiver-side is sterile normal saline solution, which is adjusted to approximate the tonicity of the buffer solution on the donor-side. One milliliter of the drug solution is pipetted onto the donor-side of the skin and 50 microliter aliquots are withdrawn from the receiver-side at the various time intervals. These samples are injected onto an HPLC column under the aforementioned conditions.

The donor solutions are prepared as 1.0 M (approximately 20% W/V) arecoline hydrochloride or arecoline hydrobromide in a phosphate, citrate, borate buffer adjusted to various pH values. Each flux experiment is repeated three to five times.

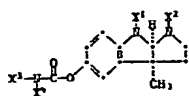
Having now fully described the invention, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the invention as set forth herein.

CLAIMS

1. A device for treating memory impairment comprising an effective amount of a compound selected from formula I,

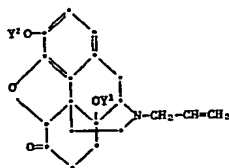


wherein R¹ represents hydroxy, lower alkoxy, or NR³R⁴ and R², R³ and R⁴ independently represent hydrogen or lower alkyl; formula II,



(II)

wherein X^1 , X^2 , X^3 and X^4 , independently represent hydrogen or lower alkyl; formula III,



(III)

wherein Y^1 and Y^2 independently represent hydrogen, lower alkyl or lower alkanoyl; and formula IV,



(IV)

5 wherein Z represents hydrogen or lower alkyl; and a means for delivering the compound at a continuous, controlled rate.

2. A device according to claim 1 wherein the device delivers the active agent transdermally.

10 3. A device according to claim 1 wherein the device delivers the active agent orally.

4. A device according to any preceding claim wherein the compound is arecoline.

5. A device according to any of claims 1 to 3 wherein the compound is physostigmine.

15 6. A device according to any of claims 1 to 3 wherein the compound is naloxone.

7. A device according to any of claims 1 to 3 wherein the compound is nicotine.

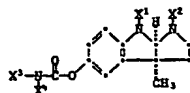
20 8. A device according to any preceding claim wherein the compound is combined with a suitable excipient.

9. A device according to claim 1 wherein the compound is a mixture containing 2-40 parts by weight of a compound of formula I,



(I)

wherein R^1 represents hydroxy, lower alkoxy, or NR^3R^4 and R^2 , R^3 and R^4 independently represent hydrogen or lower alkyl, and 1 part by weight of a compound having formula II,



(II)

30 wherein X^1 , X^2 , X^3 and X^4 , independently represent hydrogen or lower alkyl.

10. A device according to claim 9 wherein the mixture contains 4-30 parts by weight of the compound having formula I.

35 11. A device according to claim 9 wherein the mixture contains 6-20 parts by weight of the compound having formula I.

12. A device according to claims 9 to 11 wherein the compound having formula I is arecoline and the compound having formula II is physostigmine.

13. A device according to any preceding claim further comprising an anticholinergic agent in an amount to reduce cholinergic side effects wherein the anticholinergic agent does not cross the blood brain barrier.

14. A device according to claim 13 wherein the anticholinergic agent is methscopolamine.

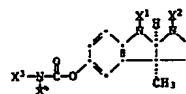
15. A device according to claim 13 wherein the anticholinergic agent is homatropine methyl bromide.

16. The use of a compound selected from formula I,



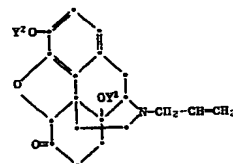
(I)

wherein R^1 represents hydroxy, lower alkoxy, or NR^3R^4 and R^2 , R^3 and R^4 independently represent hydrogen or lower alkyl; formula II,



(II)

wherein X^1 , X^2 , X^3 and X^4 , independently represent hydrogen or lower alkyl; formula III,



(III)

wherein Y^1 and Y^2 independently represent hydrogen, lower alkyl or lower alkylcarbonyl (lower

60 alkanoyl); and formula IV,



(IV)

wherein Z represents hydrogen or lower alkyl for the manufacture of a device according to claim 1 for treating memory impairment.

17. A process for the manufacture of a device according to claim 1.

18. A method for treating memory impairment comprising administering to a patient in need of such an administration a device according to claim 1.

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